Component-Based Syntheses of Trioxacarcin A, DC-45-A1 and Structural Analogues

Substrate-Directable Electron-Transfer Reactions. Dramatic Rate Enhancement in the Chemoselective Reduction of Cyclic Esters Using SmI₂–H₂O: Mechanism, Scope, and Synthetic Utility

SYNTHESIS/SYNLETT Editorial Board Focus: Professor Xue-Long Hou (Shanghai Institute of Organic Chemistry, P. R. of China)

Chemoselective Oxidative C(CO)–C(methyl) Bond Cleavage of Methyl Ketones to Aldehydes Catalyzed by Cul with Molecular Oxygen
Dear Readers,

This issue of *SYNFORM* is introduced by the impressive and unprecedented synthesis of trioxocarcins, which are highly potent antiproliferative natural compounds having remarkably complex structure, achieved by Professor Andrew G. Myers (USA). This synthetic masterpiece is the result of eight years of work, throughout which the Myers group achieved first the synthesis of the common aglycon and then crowned their work with this convergent and highly effective route to trioxocarcins and their structural analogues. The second *SYNSTORY* comes from the P. R. of China and covers the work conducted by Professor Xihe Bi in the area of chemoselective oxidations. The Chinese researchers developed an efficient and mild Cu(I)-catalyzed process employing O₂ as the oxidant for transforming methyl ketones into aldehydes, which may find significant applications in organic synthesis. The next *SYNSTORY* reports on another chemoselective process, but this time a reduction: the samarium (II) iodide promoted conversion of cyclic esters into diols developed by Professor David Procter and Dr. Michal Szostak (UK). The issue is completed by an interview with Professor Xue-Long Hou, who joined the *SYNTHESIS* editorial board three years ago as a regional editor.

Enjoy your reading!

Matteo Zanda
Editor of *SYNFORM*

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**CONTACT 📩**

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The first trioxacarcins, including trioxacarcin A (Figure 1), were isolated in 1981 by Tomita et al. (*J. Antibiot.* 1981, 34, 1519) from the soil bacterium *Streptomyces bottropensis* DO-45. Many of these molecules, particularly trioxacarcin A, displayed strikingly potent antiproliferative effects in human cancer cell lines, as well as antibacterial and antimalarial activity. Studies of the trioxacarcins appeared primarily in the patent literature in the 1990s. Professor Andrew G. Myers from Harvard University (Cambridge, MA, USA) said: “To our knowledge, trioxocarcins were not the subject of any synthetic work at that time.” However, later in the 2000s, seminal studies by researchers at the University of Göttingen (Germany) made clear that trioxacarcins covalently modify duplex DNA (*Nucleic Acids Res.* 2008, 36, 3508; *Anal. Bioanal. Chem.* 2008, 390, 1139).

In 2005, the group of Professor Myers began research to develop a short, convergent, and component-based route that would allow for rapid synthesis of trioxacarcins, broadly defined.

Professor Myers said: “In 2011 we completed the synthesis of DC-45-A2, the aglycon common to the trioxacarcin class (Figure 1), by the assembly of three components of similar synthetic complexity (*Proc. Natl. Acad. Sci.* 2011, 108, 6709).” This synthetic route comprised a scheme for differential hydroxyl protection which the Harvard-based scientists imagined would enable selective functionalization of each of the free hydroxyl groups within DC-45-A2. Professor Myers continued: “Our report in *Nature Chemistry* represents a realization of this strategy and permits the incorporation of the two final components of our route, the glycosyl residues tri-
oxacarcinose A and trioxacarcinose B. By adhering strictly to a strategy of late-stage convergent coupling reactions we believe we have enabled a truly modular, component-based synthesis.” Using this route, Professor Myers and co-workers prepared the glycosylated trioxacarins DC-45-A1 and trioxacarcin A (Figure 1) and more than 30 structural analogues, which they obtained by modification of four of the five building-block compounds.

The key challenge addressed in the report is the selective coupling of the glycosyl residues to the trioxacarcin aglycon (Scheme 1). “We found that Lewis acid promoted glycosylation of aglycon substrates proceeded cleanly despite the high density of oxygenated functions present within the aglycon, which includes adjacent dimethyl acetal, ketal, hemiketal, and spiro epoxide functions,” explained Professor Myers. The aglycon is stable to treatment with excess N-trimethylsilyl bis(trifluoromethanesulfonate) or trimethylsilyl trifluoromethanesulfonate, reagents which were required to promote glycosylation of the unreactive C13 hemiketal. Professor Myers added: “We were pleased to find that both glycosidic couplings were fully $\alpha$-selective, which we believe is explained by stereoelectronic and steric effects, as discussed in the article.”

The group found that in order to prepare the doubly glycosylated precursor to trioxacarcin A, it was necessary to employ a glycosylation methodology that used a soft Lewis acid for activation, so-called orthogonal conditions to those used in the first glycosylation, which was promoted by hard Lewis acids. They made use of reaction conditions originally developed by Hirama (Angew. Chem. Int. Ed. 2001, 40, 946), and this coupling, too, was fully $\alpha$-selective (Scheme 2).
It is noteworthy that opening of the spiro epoxide function was not observed at any point during Myers’ synthetic route to trioxacarcin A, which also took advantage of the wide range of reactivities exhibited by the various hydroxyl groups – for example, it was not necessary to protect either of the two tertiary alcohols present within the two sugar residues.

Scheme 3 shows the convergent nature of Professor Myers’ synthesis, with vertical arrows denoting convergent coupling reactions, while linear or non-convergent steps are indicated by horizontal arrows. Colored circles are used to represent each of the five components of similar complexity used to assemble trioxacarcin A, and other synthetic intermediates (structures not shown) are represented with grey circles. Professor Myers commented: “We have found it useful to analyze and display other synthetic routes developed in the group in the same manner.”

“We had anticipated that a convergent, component-based route would enable synthetic access to trioxacarcins in the broadest possible sense,” said Professor Myers. “We were able to introduce significant structural changes through modification of four of the five modular components either individually or in combination.” For many of these analogues, no changes to the synthetic route were required other than to use the appropriate modified component, and even in the most difficult cases only small changes were required. The rapidity...
with which this group of analogues was assembled speaks to the generality of the key convergent couplings and of the route in general. Professor Myers remarked: “Upon submission of our manuscript we had prepared more than 30 novel trioxacarcins; we expect this quantity to increase steadily and it has exceeded 50 as of the time of writing this article.”

“We believe that the trioxacarcins have great potential for use as cytotoxic payloads in antibody–drug conjugates, and we are actively pursuing studies along these lines,” said Professor Myers. He concluded: “A noteworthy property of the trioxacarcins with respect to biological evaluation is that they are strongly fluorescent molecules, allowing for non-perturbative visualization in any number of contexts. In the future, we also seek to study how and why structural modifications of the trioxacarcins produce changes in their biological activity.”

About the authors

Thomas Magauer was born in Linz (Austria) in 1983. He grew up in Steyr and moved to Vienna in 2002 to study chemistry at the University of Vienna (Austria). In 2007, he joined the laboratories of Professor Johann Mulzer and under his guidance he developed enantioselective syntheses of the complex polyketide kendomycin and the sesquiterpenoid echinopines A and B. After graduating in 2009, he moved to Harvard University (USA) to begin postdoctoral studies with Professor Andrew G. Myers. At Harvard University he developed a synthesis of natural and diverse unnatural trioxacarcins. In 2012, he started his independent research as a Liebig junior research group leader at the LMU Munich (Germany). In 2013, he was awarded the Emmy Noether fellowship by the DFG.

Daniel J. Smaltz grew up in Paxton, MA (USA). He received his B.Sc. degree in chemistry from Worcester Polytechnic Institute (USA) in 2009. During his undergraduate years he conducted research in synthetic organic chemistry with Michael Hearn at Wellesley College (USA) and James Dittami at Worcester Polytechnic Institute. Daniel then began graduate studies at Harvard University (USA), studying the synthesis and biological evaluation of trioxacarcins in the laboratory of Andrew G. Myers.

Andrew G. Myers received his B.Sc. from the Massachusetts Institute of Technology (Cambridge, USA) in 1981, and went on to pursue graduate studies with Professor Elias J. Corey at Harvard University (USA). He started his independent career at the California Institute of Technology (Pasadena, USA) in 1987, and moved to Harvard University in 1998, where he is currently Amory Houghton Professor of Chemistry. His research program involves the synthesis of complex molecules of importance to human medicine. He and his students have also developed methods of general utility in the construction of complex molecules.
Aldehydes are important building blocks in organic synthesis and are utilized broadly as starting materials to construct complex structures. Oxidation of alcohols is probably the method most used for synthesizing aldehydes, but while numerous oxidation methods have been developed, only a few are used routinely. The development of new and efficient processes for producing aldehydes with safe reagents under mild conditions is therefore still highly desirable and valuable. Recently, Professor Xihe Bi and co-workers at Northeast Normal University (Changchun, P. R. of China) have reported a novel Cu-catalyzed oxidative C(CO)–C(methyl) bond cleavage of methyl ketones to aldehydes using molecular oxygen as the oxidant with only hydrogen and carbon dioxide as the by-products (Scheme 1).

The selective cleavage of C–C \( \alpha \)-bonds by transition-metal complexes has received considerable attention in the past two decades, not only due to the fundamental challenges connected with the process, but also to its potential utility in organic synthesis. Accordingly, many research efforts have been focused on developing new methodologies for achieving that transformation. Very recently, Jiang and co-workers described an interesting oxidative cleavage and esterification of the C–C bonds of \( \alpha \)-hydroxy ketones under metal-free conditions (Angew. Chem. Int. Ed. 2012, 51, 12570), and the Cu-catalyzed aerobic oxidative esterification reaction of 1,3-diones has been reported by the Jiao group (J. Am. Chem. Soc. 2013, 135, 15257). However, the selective oxidative cleavage of C–C \( \alpha \)-bonds still remains one of the most challenging issues in chemistry and biology.

Professor Bi remarked: “Looking back at the very beginning of this project, our study commenced with the reaction of \( \alpha \)-acetonaphthone and molecular oxygen catalyzed by a variety of copper salts under different conditions. To our delight, a 92% yield of the \( \alpha \)-naphthaldehyde could be achieved with a copper catalyst as a result of an oxidative C(CO)–C(methyl) bond cleavage.” According to Professor Bi, when the reaction was carried out in deuterated dimethyl sulfoxide and monitored by in situ \(^{13}\)C NMR spectroscopy, no other products were detected; hence, it could be concluded that hydrogen and carbon dioxide are the only by-products in this reaction.
Divergently substituted aryl, heteroaryl and aliphatic methyl ketones were subjected to the optimized conditions, resulting in a range of aldehydes as shown in Scheme 2. “The results indicate that neither electron-withdrawing nor electron-donating groups have any influence on the course of the reaction providing the corresponding products in good to excellent yields,” said Professor Bi.

Preliminary mechanistic studies disclosed an interesting reaction sequence involving α-oxygenation/hydration/1,2-hydride shift/C–C bond cleavage. Professor Bi explained: “It has been found that the oxidation of a methyl group is more favorable than that of a methylene moiety. Also, it implies that the cleavage of the C(CO)–C(methyl) bond of methyl ketones should be the rate-limiting step in the degradation of aliphatic methyl ketones.”

Professor Xihe Bi concluded: “This oxidative cleavage of the C(CO)–C(methyl) bond of methyl ketones represents an efficient method for the synthesis of various aldehydes, which holds promise for finding wide applications in organic synthesis. Further mechanistic understanding and methodological exploration will likely advance the synthetic usefulness of this class of reactions and bring increased attention to this challenging area of C–C bond cleavage.”
Electron-transfer reactions with low-valent metal reagents are among the most important processes in organic synthesis. Since 2011, Dr. Michal Szostak and Professor David Procter at the University of Manchester (UK) have been studying the activation of SmI₂ reagents with Lewis bases for the reduction and reductive cyclizations of unactivated esters, substrates which due to their high redox potential are particularly challenging to chemoselectively manipulate under single-electron-transfer conditions (Chem. Commun. 2011, 47, 10254; see also J. Am. Chem. Soc. 2008, 130, 1136). It was found earlier that the activation of Sm(II) with the H₂O co-solvent, used typically in high concentrations, allows unprecedented selectivity in transformations of cyclic six-membered esters in that other cyclic and acyclic esters were not reduced with this reagent system. “We have extended this concept to several other functional groups that are typically unreactive towards SET reactions (Chem. Soc. Rev. 2013, 42, 9155). However, for a long time, the chemoselective activation of carboxylic acid functional groups other than six-membered lactones seemed to lie outside the reducing range of the SmI₂–H₂O reagent.”

A key observation that led to the current study was that the reduction of several substrates decorated with polar functional groups proceeded faster than in the absence of polar moieties. This led to an early hypothesis that directing groups on the substrate would coordinate to the reactive Sm(II) complex and increase the rate of electron transfer in the rate-determining step of the reaction via an ordered transition state. “To put

![Scheme 1](image-url)

**Scheme 1** The chemoselective reduction of lactones with SmI₂–H₂O enabled by the directing group effect and the rate enhancement study.
this idea into practice, first we needed to develop robust protocols for the synthesis of SmI₂ (J. Org. Chem. 2012, 77, 3049; Nat. Protoc. 2012, 7, 970). Early in the studies it became evident that Sm(III) impurities often present in the reagent result in undesired oxidation of the solvated Sm(II) complexes. Interestingly, it was found that SmI₂ is a much more user-friendly reagent than is currently believed, and its preparation does not require special precautions provided that high-quality Sm metal is used for the synthesis.

“With this background we determined the effect of thermodynamic rate enhancement in the reduction of lactones having strategically positioned directing groups.” Remarkably, several directing groups promoted the reduction of five- and seven-membered lactones with the SmI₂–H₂O reagent, while retaining high levels of chemoselectivity in that an array of carboxylic acid based functional groups were readily tolerated under the reaction conditions even when excess of the reagent was present. In collaboration with Bob Flowers of Lehigh University (Bethlehem, Pennsylvania, USA), an expert in the field of mechanistic lanthanide(II) chemistry, we were able to quantify the effect of directing groups on the reduction of lactones. Notably, in some cases a rate of acceleration in excess of six orders of magnitude was found by simply placing a directing group in close proximity to the lactone carbonyl.

The present reaction is remarkable because it demonstrates for the first time that directing groups can be used to activate inert functional groups towards radical reactions mediated by low-valent metals. “The dramatic rate enhancement through the application of directing groups illustrates the importance of lowering activation entropy (chelation) to achieve successful electron transfer. The acyl-type radicals generated from lactones of various ring sizes serve as precursors for the stereocontrolled synthesis of carbocycles via reductive cross-coupling.” The concept will have intriguing applications in target-oriented synthesis because it significantly expands the scope of Sm(II)-mediated cascade cyclizations to construct various ring systems for the synthesis of complex terpenes. “Ultimately, we believe that the expansion of the scope of directing groups and further mechanistic studies will result in a suite of novel radical reactions that are calibrated by the rational design of lanthanide(II) reductants (Angew. Chem. Int. Ed. 2013, 52, 7237; Angew. Chem. Int. Ed. 2012, 51, 9238). The formalization of the directing-group concept in electron-transfer chemistry paves the way to initiate its application to achieve remarkable chemoselectivity in a plethora of Sm(II) and other electron-transfer reactions.”

About the authors

Michal Szostak received his Ph.D. from the University of Kansas (USA) in 2009 under the supervision of Professor Jeffrey Aubé. After postdoctoral research at Princeton University (USA) with Professor David MacMillan, he joined the group of Professor David Procter at the University of Manchester (UK). His research interests include the development of new lanthanide(II) reductants and various aspects of transition-metal-mediated free-radical chemistry.

Dr. M. Szostak

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Malcolm Spain received his MChem degree in 2010 at the University of Manchester. He is currently conducting Ph.D. research under the supervision of Professor David Procter at the University of Manchester. His work involves the development of new transformations using SmI₂ and H₂O.

David John Procter received his Ph.D. from the University of Leeds (UK), working with Professor Christopher Rayner. After postdoctoral work with Professor Robert Holton at Florida State University (USA) working on Taxol®, he took up a Lectureship at the University of Glasgow (UK). After moving to the University of Manchester, David was promoted to Professor in 2008. He is currently Head of Organic Chemistry and a Leverhulme Research Fellow. His research interests lie in the development of organic reactions and their application in biology, medicine and materials science. David is joint author of the research text "Organic Synthesis using Samarium Diiodide".
SYNFORM will from time to time portrait SYNTHESIS/SYNLETT Editorial and Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. In this issue, we present Professor Xue-Long Hou from Shanghai Institute of Organic Chemistry, P. R. of China.

**INTERVIEW**

**SYNFORM | What are your main current research interests?**

**Prof. X.-L. Hou** Working in the fields of organometallic chemistry directed towards organic synthesis and organocatalysis, especially the design of chiral ligands and their applications in asymmetric catalysis.

**SYNFORM | What is your most important scientific achievement to date and why?**

**Prof. X.-L. Hou** In the Pd-catalyzed asymmetric allylic alkylation reaction, we designed and synthesized a series of ferrocene-based P,N-chiral ligands, named as SIOCPhox. With these ligands, we have tried to address some challenges present in the field. For example, excellent regio- and enantioselectivities in the palladium-catalyzed allylic substitution reaction with a wide range of mono-substituted allylic substrates and polyenyl substrates have been realized.

With these ligands, a series of ‘hard’ carbanions have been used successfully as nucleophiles in palladium-catalyzed asymmetric allylic substitution reactions, leading to highly enantioselective allylic alkylation of nucleophiles derived from acyclic ketones, carboxylic amides and acylsilanes. Two chiral centers were also installed in acyclic ketones and acylsilanes with excellent regio-, diastereo- and enantioselectivities.

Under palladium-catalyzed allylic substitution reaction conditions, highly enantioselective cyclopropanation has been realized, which is considered as a major breakthrough in the field. Kinetic resolution of carbon and nitrogen nucleophiles by the palladium-catalyzed allylic substitution reaction has also been achieved.

Using FePhoX and modified derivatives thereof (by changing the substituent on the phenyl ring attached to the P atom of FePhoX), we developed a new strategy to realize a switch of diastereoselectivity by tuning the electronic effect of the ligands in the copper-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with nitroalkenes and the Mannich reaction of azomethine ylide with tosyl imines.
SYNFORM | Do you have hobbies, besides chemistry?

Prof. X.-L. Hou | I like classical music very much. Every time the music will give you a nice mood. When you are tired, the music will let you relax; when you prepare to work, the music will give you passion...

Matteo Zanda
FURTHER HIGHLIGHTS

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(by T. K. Olszewski)

SYNLETT
Account on: Synthesis of Oligobenzamide α-Helix Mimetics
(by G. M. Burslem, A. J. Wilson)

SYNFACTS
Synfact of the Month in category “Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions”: Enantioselective [3+2] Annulation via C–H Activation Catalyzed by Iridium

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